

Testicular regression syndrome — a pathological study of 77 cases

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Testicular regression syndrome is characterized by a rudimentary epididymis and spermatic cord with absence of testicular tissue. Although it has been well-described in the surgical literature, few pathological studies have been performed. We report 77 cases of the syndrome, deriving from a 26-year retrospective review. Typical gross descriptions described several cm of spermatic cord with a small mass of firm, fibrotic tissue at one end; elements of the vas deferens, spermatic artery and venous plexuses were usually present. Histologically, the distal expansion of most of the specimens was composed of dense fibrovascular tissue with no evidence of seminiferous tubules or normal testicular elements. Instead, scattered foci of calcification and brown pigment were present. The finding of dystrophic calcification and haemosiderin deposition, with no evidence of viable testicular tissue, in the presence of relatively normal spermatic cord elements, supports the concept of generally unilateral and occasionally bilateral anorchia secondary to remote infarction. The young age of the patients, coupled with the history of an absent testis from birth, is supportive of *in utero* damage. These histopathological findings provide support for the concept of *in utero* torsion of the testis as the basis for the testicular regression syndrome.

Keywords: testicular regression, secondary anorchia, infarction

Introduction

Testicular regression syndrome ('vanishing testis' syndrome) is defined as the unilateral and bilateral partial and complete absence of testicular tissue with or without rudimentary epididymal and spermatic cord remnants, in the presence of normal internal duct development and normal external genitalia¹. Although testicular regression syndrome is well-described in the paediatric surgical literature¹, little has been written on its histopathological features. As it is an important part of the clinical differential diagnosis of cryptorchidism, with up to 3-20% of boys with impalpable testes showing complete absence when surgically explored^{2,3}, the following 26-year retrospective review was undertaken to further define the morphological features.

Materials and methods

The computerized files of the Department of Histopatho-

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logy at the Adelaide Children's Hospital were reviewed and all cases between January 1964 and June 1990 with a clinicopathological diagnosis of testicular regression were obtained. Request forms were retrieved and clinical data relating to age at operation and side(s) affected were collated. Histological slides were reviewed and Perls' and Schmeltzer's stains were performed⁴.

Results

There were 476 orchidectomy specimens on file, of which 77 (16.2%) were diagnosed as testicular regression syndrome. Analysis of these 77 cases showed that the ages of patients ranged from 2 months to 15 years 10 months (mean 4 years 4 months). The left side was affected in 53 cases (69%), the right in 22 (28%) and two cases (3%) were bilateral. The difference in prevalence between left and right is statistically significant; χ^2 (one degree of freedom) = 12.81, $P < 0.001$.

Tissue identifiable as vas deferens, epididymis or seminiferous tissue was present in 64 cases (83%). Vas deferens were most frequently found, in 61 cases (79%),



Figure 1. Epididymal tissue in loose stroma and vas deferens elements with prominent concentric smooth muscle. H & E.

and epididymis was seen in 28 (36%) (Figure 1). In only three of these 28 cases with epididymis was there no accompanying vas deferens. Small groups of seminiferous tubules in fibrous stroma (Figure 2, inset) were found in three cases (4%) and epididymal tissue was present in these cases. In two cases (3%) a well-demarcated, discrete fibrous nodule was seen. Twelve specimens lacked identifiable genital tissue but, in six of these, areas of calcification and/or iron pigmentation were present. Calcium deposits were noted in a total of 32 cases (42%), and in nine of these (12%) an associated giant cell reaction was present. Iron pigment was present in 32 cases (42%), with an associated giant cell response noted in two (3%). The combination of pigment and calcium (Figure 2) was present in 26 cases (34%) and six cases (8%) each showed either pigment alone or calcification alone.

A fibrous stroma was present in all cases. Other tissues noted were arteries and veins (66/77, 86%), venous

elements alone (12/77, 16%), adipose tissue (34/77, 44%), nerves (43/77, 56%) and atrophic voluntary muscle (44/77, 57%). The iron pigment stained both for ferrous and ferric ions using Perls' and Schmeltzer's stains⁴. Electronmicroscopy was performed in two cases and showed the typical appearance of haemosiderin⁵. In six cases (8%) a vascular fibrous stroma was present.

Discussion

Gonadal differentiation in man commences at the completion of the migration of primordial germ cells from the yolk sac to the gonadal ridges on the surface of the mesonephros. If a Y chromosome is present in the germ cells, tubular rather than follicular formations develop and Sertoli cells appear by induction of the surrounding somatic blastema. Extragonadal masculine development including differentiation of Wolffian ducts and genital sinuses is induced by testosterone secreted by

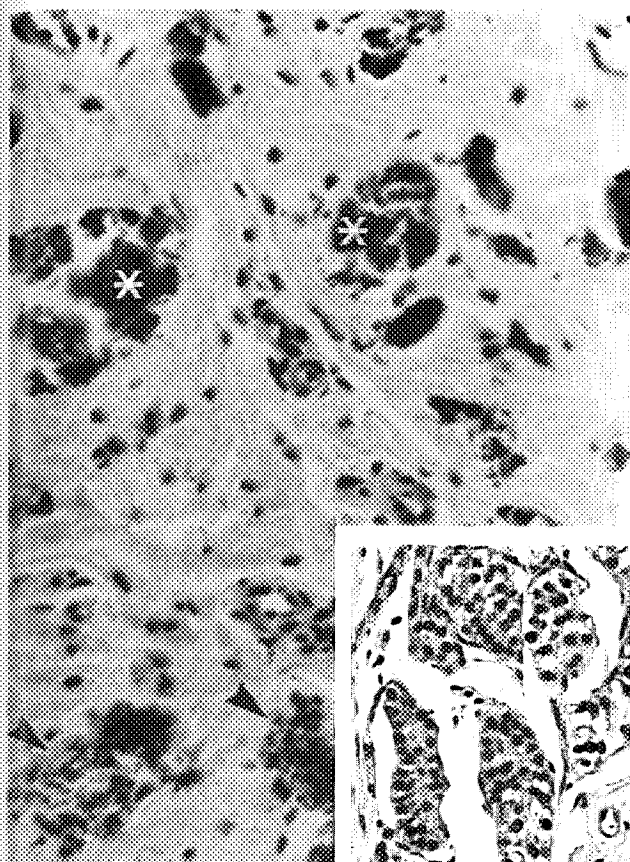


Figure 2. Calcific debris (*) and iron pigment (arrowheads). Inset: Atrophic seminiferous tubules in loose fibrous stroma.

the Leydig cells and is established at 16 weeks of gestation. Prior to this sequence, Müllerian inhibiting factor from Sertoli cells blocks the development of Müllerian ducts to female reproductive ducts. This has been shown to be the first event in male sexual differentiation⁶.

The clinical presentations of testicular regression can be correlated with the embryological sequence and grouped into early and late embryonic, and early, mid and late fetal or early neonatal events^{2,7}. It is the latter two groups with which the current study is concerned. These are genotypically XY infants with unambiguous male external genitalia, normal Wolffian development and rudimentary Müllerian structures. They present with unilateral or, less commonly, bilateral anorchia. It has been suggested that testicular loss occurs during descent, which occurs in the last month of fetal life, by mechanisms which include torsion or vascular occlusion similar to those which affect cryptorchid testes^{8,9}. Other studies suggest that regression occurs prior to the formation of the tunica albuginea at 15–16 weeks of gestation as a result of spermatic vein thrombosis¹⁰.

Testicular loss in the neonatal period is reported³. The site of termination of the vas deferens or position of the remaining epididymal tissue may indicate the point at which loss of testis occurred and if the testicular vessels are found to accompany the vas and terminate with it, there is little likelihood that a testis lies elsewhere in the pathway of descent⁹. The intimate relationship between epididymal and testicular development means that the testis can be assumed to be absent if vas and epididymis are found within the scrotum, and the testis is not in the inguinal canal⁹. This is of considerable clinical significance, as the differential diagnosis of secondary anorchia includes primary agenesis or dysgenesis of the testis, a finding which indicates the need for genotypic studies, and maldescent, with an associated increased risk of malignancy in the cryptorchid testis¹¹. Some authors advocate surgical fixation of the contralateral testis to reduce the risk of torsion of remaining testicular tissue².

The histological findings in testicular regression syndrome are characteristic, if non-specific. Honore¹⁰ found vas deferens in all of eight paediatric cases studied and epididymis in two of these. Distal tissues consisted of fibrous tissue, nerves, muscle and vascular elements. In one case evidence of calcification and siderophages was noted. Of six cases, Heller *et al.*¹² noted vas deferens in five, epididymis in five, vas deferens or epididymis alone in one case and spermatic tubules in one case. Fibrous tissue rich in elastic fibres, blood vessels and nerve fibres only were noted by Salle *et al.* in their two cases¹³. In a series of 21 cases (A. Sparnon, personal communication), vas deferens was noted in 18, epididymis in 12, calcification in 11, pigmentation with iron compounds in eight, muscle in 16 and large blood vessels in 17. Similar results were reported by Wright². We noted vas deferens, epididymis, calcification or haemosiderin pigmentation in 71 of 77 cases (92%). Testicular remnants could not be histologically confirmed in the remaining six cases (8%), but clinical and surgical findings and the presence of a richly vascular stroma supported the diagnosis¹³.

It has been suggested that the preterm testis is particularly susceptible to haemorrhagic infarction once the fibrous tunica albuginea has formed, due to the large number of thin walled vessels and relatively sparse loose stromal connective tissue. As the fetal response to infarction may include fibrosis and calcification with little inflammation it is not surprising that calcification is seen in some of this tissue¹. If haemorrhage is extensive at the time of infarction a large accumulation of iron-containing blood pigment may also occur and be reflected in post-natal life as haemosiderin pigment in the fibrous remnant of infarcted tissue.

Honore¹⁰ found that the left testis was more suscep-

tible to regression, and our study concurs with this impression, with 68% of cases being left-sided. Burge¹⁴ found 18 of 30 cases (60%) to be left-sided. It has been suggested that the anatomical arrangement of the left spermatic vein, draining into the left renal vein, may predispose to kinking, due to an unusually mobile left kidney. As there is no venous anastomosis across the midline until after 16 weeks, venous infarction may result¹⁰. This theory would not account for right-sided or bilateral cases, and so other factors must also be involved.

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